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(54) Title: PHARMACEUTICAL FORMULATION AND A METHOD OF MAKING SAME

(57) Abstract: The methods of the present invention and the formulations made from those methods, allow the stable integration of multiple actives within a single formulation. The solubilisation of an active in a suitable solvent and the subsequent adsorption onto a sorbing medium provide effective protection for the active from any adverse conditions within the liquid in which the active-loaded sorbing medium is dispersed. As a result the liquid can be formulated to suit the requirements of the actives that may include therein. As a result the actives may be stably integrated within the formulation.

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Pharmaceutical Formulation and a Method of Making Same

FIELD OF THE INVENTION

This invention relates to pharmaceutical formulations, their preparation and their use in veterinary applications.

- 5 More specifically, the present invention relates to methods of making multi-active formulations which are capable of stably integrating multiple actives.

BACKGROUND

- It is often desirable to administer a combination of actives. A mixture may be required for effective management of a condition, or the combination may give an advantageous result over
10 the administration of a single active.

- In most human health situations the administration of multiple formulations is acceptable. However, in circumstances where mass administration of a combination of actives is required, it is advantageous if the combination can be administered in the same formulation. This is especially the case where inoculating a large proportion of the population or in the veterinary
15 applications where a herd of animals may require treatment.

In some cases, the actives to be co-administered will have overlapping formulation requirements and should to co-exist stably in the formulation.

- However, in many cases, the actives to be co-administered will have conflicting formulation requirements or may actively degrade each other. By way of example, levamisole is soluble in
20 water-based formulations and requires an acidic pH for stability. By contrast avermectins are substantially insoluble in water. If formulated in water based formulation avermectins require a neutral pH for stability. In the acid pH required by levamisole the avermectins will degrade.

In addition, to the need for finding a formulation in which each of the actives can stably integrate, the formulation must be practical to use. That is, it must be able to be stored for say up to a year without significant physical or chemical changes taking place. The relative proportions of the components should not change significantly over time. In addition, while
5 some sedimentation is to be expected, the sediment should be easily re-dispersed on shaking. The formulation should not cause excessive side effects in the animal. The formulation should be relatively easy to administer and it is of suitable flowability to allow delivery by injection and drench.

Various attempts have been made to produce effective combined active formulations with
10 limited success.

One such attempt is set out in New Zealand Patent Application No. 336139, which involves a storage stable veterinary composition comprising a levamisole containing aqueous phase and an anthelmintic containing organic phase wherein the composition having at least most of the first active in the organic phase is emulsified in the second liquid phase which includes the second
15 active agent when present. However, this suspo-emulsion method, as it is known, tends to result in a formulation that is highly viscous and flows poorly. As such, it is difficult to administer.

Accordingly there is a need for an improved formulation capable of integrating a number of actives together with a method of manufacturing the same.

OBJECT

20 It is the object of the present invention to provide an improved multi-active formulation and a method of making the same or one that will at least provide the public with a useful choice.

STATEMENT OF THE INVENTION

In one aspect the invention comprises a method of manufacturing a pharmaceutical formulation comprising the steps:

- 25 a) Dissolving an active in a solvent;
- b) Sorbing the solvent containing active composition on to a sorbing medium; and then

c) Dispersing the sorbing medium loaded with the solvent composition in a liquid.

Preferably the active is a lipophilic active.

More preferably the lipophilic active is selected from the group including the avermectins and the milbemycins.

5 Preferably the liquid is an aqueous vehicle.

Preferably the solvent is selected from oils and organic solvents.

More preferably the solvent is selected from medium chain mono-/di-glycerides (Capmul MCM) in the range of 0.1-10% preferably between 2-4%.

10 Preferably the liquid optionally includes one or more medicaments selected from the group including vitamins, minerals, anthelmintics or antigens.

Preferably the minerals are selected from selenium salts, cobalt salts, copper salts, zinc salts and iodine salts and their chelates.

More preferably the minerals are sodium selenate and cobalt EDTA.

15 Preferably the anthelmintics are selected from the group including thiazole derivatives such as a levamisole salt and benzimidazole derivatives such as albendazole, oxfendazole, fenbendazole, mebendazole and acylated quinoline such as praziquantel and benzenesulphamide such as clorsulon and closantel.

20 More preferably the sorbing medium is selected from magnesium aluminometasilicate, cellulose, microcrystalline cellulose, diatomaceous earth, montmorillonite, bentonite, titanium dioxide, amorphous silicon dioxide, colloidal silicon dioxide, calcium carbonate, talc (SiO₂+MgO), attapulgite (silicon, aluminium and iron oxides clay), kaolin (aluminium silicate) preferably colloidal silicon dioxide (Aerosil) more preferably Aerosil R972.

Preferably the liquid optionally comprises further excipients including but not limited to preservatives, suspending agents, buffering agents, antifoaming agents and the like.

In a further related aspect the invention comprises a pharmaceutical formulation capable of dilution and capable (with or without dilution) of being administered to an animal, said formulation comprising:

- 5 a) an active dissolved in a suitable solvent to form a solution and sorbed on to a sorbing medium; and
- b) Preferably including an liquid diluent.

Preferably the active is a lipophilic active.

Preferably wherein the active is selected from the group including the avermectins and the milbemycins.

- 10 Preferably the solvent is selected from oils and organic solvents.

More preferably the solvent is medium chain mono-/di-glycerides (Capmul MCM).

Preferably the liquid diluent is an aqueous vehicle.

More preferably the liquid diluent optionally includes one or more additional medicaments selected from the group including vitamins, minerals, anthelmintics or antigens.

- 15 Preferably the medicament is either soluble and/or dispersible in the liquid.

Preferably the minerals are selected from wherein the minerals are selected from selenium salts, cobalt salts, copper salts, zinc salts and iodine salts and their chelates.

More preferably the minerals are selected from sodium selenate and cobalt EDTA.

- 20 Preferably the anthelmintics are selected from the group including thiazole derivatives such as a levamisole salt and benzimidazole derivatives such as albendazole, oxfendazole, fenbendazole, mebendazole and acylated quinoline such as praziquantel, and benzenesulphonamide such as a clorsulon and closantel.

Preferably the formulation additionally includes preservatives, suspending agents, buffering agents, antifoaming agents and the like.

In a further related aspect the invention relates to a method of medical treatment comprising administering a formulation as described in the preceding statements to an animal.

- “Solvent” means an oil or water immiscible liquid having good solubility for the active and being able to sorb onto the silica or other sorbing medium to physically separate the first active from the liquid.

“Sorb and sorbing” is used to include the absorption and adsorption processes.

“Active” includes compounds which provide a health advantage or benefit to an animal to which the formulations referred to in the above paragraph are administered. Active includes vitamins, minerals, anthelmintics, antigens and the like.

- “Liquid” referred to in the preceding paragraphs comprises a liquid carrier optionally including one or more actives dissolved or suspended therein. The liquid may be water or oil based liquid.

- In preferred examples the liquid will be an aqueous vehicle, that is it will be water based and will include a water soluble active dissolved therein. It is envisaged however that the liquid may also include a further active suspended therein.

The liquid may also include excipients including defoaming agents and buffering agents.

The method requires the dissolving of a first active in a suitable solvent. This solution is sorbed onto a sorbing medium such as silica dioxide (e.g. Aerosil R972). This active loaded medium is then dispersed in a liquid.

- Suitable sorbing mediums include, by way of example, magnesium aluminometasilicate, cellulose, microcrystalline cellulose, diatomaceous earth, montmorillonite, bentonite, titanium dioxide, amorphous silicon dioxide, calcium carbonate, talc ($\text{SiO}_2 + \text{MgO}$), attapulgite (silicon, aluminium and iron oxides clay) and kaolin (aluminum silicate).

- All these exhibit large specific surface area and have high adsorption capacity and can be used to sorb the solvent-containing drug.

Hydrophobic fumed silica is also suitable for this application, as it tends to produce less viscous product when mixed with oil. The oil adsorption capacity is very good and the resulting mix is free flowing and can be dispersed easily with the bulk of the aqueous formulation.

5 The liquid in which the sorbing medium is to be dispersed may itself be a composition including an active. The liquid may comprise a water or oily based liquid and may include appropriate actives, such as levamisole, sodium selenate and the like. In addition, to the active, the liquid may include suspension aids/viscosity inducing agents such as sodium carboxy methylcellulose, guar gum, karaya gum or xanthan gum. In addition, preservatives, such as methylparaben, propylparaben and their salts may be used to prevent degradation of the formulation.

10 A defoamer, such as a silicon emulsion can be used as a lubricant.

Further, suspension aids may be incorporated within the formulation.

In addition it is envisaged the formulation method may incorporate other actives including vitamins, minerals and the like as actives. The same actives may also be dissolved in the formulation and sorbed onto the silica or other sorbing medium to provide differential release of
15 the active.

Further, it is envisaged additional avermectins or other anthelmintics may be incorporated into the formulation. These additional actives may be incorporated in the suspension or sorbed onto the silica or other sorbing medium to provide for differential release of the active.

The present invention relates to a method for making a formulation incorporating multiple
20 actives. The formulation and method are advantageous as they allow the stable integration of actives, which have different formulation requirements, in the same formulation.

The present invention is advantageous in that it allows the incorporation in a single formulation of multiple actives, which may be incompatible in that they have different solubility characteristics or requirements or they degrade the other.

25 It is important when arriving at the combination of actives and solvents to be used that the active and solvent sorbed on to the sorbing medium should be incompatible with the liquid in which the active loaded sorbing medium is dispersed. By way of example if a lipophilic active,

such as an avermectin is dissolved in a lipophilic solvent such as Capmul MCM and loaded onto Aerosil, the liquid should be an aqueous based.

An important factor in determining suitable active and solvent combinations for loading onto the Aerosil is the amount of active needed to provide effective treatment. Accordingly active
5 which provide good efficacy at relatively low dose rates are more suitable for sorption onto the Aerosil than are actives which require administration of a relatively large dose for efficacy. The constraint is a physical one, the inclusion of a larger amount of Aerosil or other sorbing medium into a formulation can lead to difficulties in flowability.

DETAILED DESCRIPTION

- 10 The present invention provides an improved veterinary composition including two or more actives together with a method of manufacturing the same.

DEVELOPMENT TRIALS

The following examples numbered 1 to 13, relate to trials to determine an effective formulation. These are given by way of illustration and shall not be taken as in any way limiting as to the
15 spirit or scope of the invention. The flow time of each example formulation that determined by timing how long it took for a volume of 100 ml to flow through a Ford no. 4 cup. A flow time of less than about 20 seconds was desired.

In addition, the chemical and physical stability of the formulation was checked. The formulations were exposed to 55°C for four weeks after which the levels of the actives and then
20 condition of the formulation was checked.

Example 1

The initial trial included silicon dioxide (brand name Aerosil R972) and polyoxyl 40 hydrogenated castor oil.

The formulation comprising:

- 25 1. 3.5g Carboxymethyl cellulose sodium is dissolved in 150ml of water.

2. 500mg Ivermectin is dissolved in 25ml of medium chain mono-/di-glycerides (Capmul MCM.)
3. 900mg Sodium methyl paraben and 100mg sodium propyl paraben are dissolved in 250ml water, wherein 476mg sodium selenate and 6.284g cobalt EDTA are added under stirring.
- 5 4. 20g Levamisole HCl is added to the formulation from step 3 under stirring, and 10g polyoxyl 40 hydrogenated castor oil and 500mg defoamer are added under stirring.
5. 11.35g Oxfendazole is dispersed into the formulation resulting from step 4 under stirring.
- 10 6. Medium chain mono-/di-glycerides containing ivermectin (the formulation from step 2) is sorbed on 15g silicon dioxide (brand name Aerosil R972) using mortar and pestle.
7. The ivermectin-loaded silicon dioxide (brand name Aerosil R972) is dispersed into the formulation of step 5 under stirring.
8. The formulation of Step 1 is added to that from step 7 under stirring.
- 15 9. 10ml of purified water is used to rinse the beaker; this is then added to the formulation from step 8.
10. The pH is adjusted to below 4, preferably 3.84 using 20%w/v citric acid solution.
11. Volume is made up to 500ml using purified water.

The result of this combination is a physically and chemically stable formulation with a flow time through a Ford No. 4 cup of 33 seconds.

Example 2

In a further trial the silicon dioxide (brand name Aerosil R972) was used alone to provide a formulation which was surfactant free.

The formulation components and method are as in example 1 except:

- At step 4 the defoamer is added but the polyoxyl 40 hydrogenated castor oil is omitted; and
- At step 10 the pH is adjusted to 3.80 instead of 3.84 in example 1

The result of this combination is a physically and chemically stable formulation with a flow time through a Ford No. 4 cup of around 27 seconds.

Example 3

In a further trial the silicon dioxide (brand name Aerosil 200) was used in combination with polyoxyl 40 hydrogenated castor oil.

The formulation components and methods are as example 1 except:

- At step 6 the medium chain mono-/di-glycerides containing ivermectin are sorbed on silicon dioxide (brand name Aerosil 200) instead of silicon dioxide (brand name Aerosil R972), and
- At step 10 the pH is adjusted to 3.76 instead of 3.84 in example 1.

The resulting formulation was chemically stable; however it exhibited a non-homogeneous sedimentation. Accordingly it was decided to discontinue this formulation. The flow time for this formulation was 28 seconds.

Example 4

In a further trial silicon dioxide (brand name Aerosil 200) was used alone to provide a formulation which was surfactant free.

- The formulation components and methods are as in example 1, except:
 - At step 4 the defoamer is added and the polyoxyl 40 hydrogenated castor oil is omitted, and

- At step 6 medium chain mono-/di-glycerides containing ivermectin are sorbed on to silicon dioxide (brand name Aerosil 200) instead of silicon dioxide (brand name Aerosil R972).
 - At step 10 the pH is adjusted to 3.81 instead of 3.84 in example 1.
- 5 • The formulation has a flow time of 17 seconds, however, it did not exhibit sufficient physical stability, accordingly it was decided to discontinue this formulation.

Example 5

In a further trial silicon dioxide (brand name Aerosil 200) and polyoxyl 40 hydrogenated castor oil were used for reconfirmation of the results in example 3.

- 10 The formulation components and methods are as example 3 except:

- At step 10 the pH is adjusted to 3.80 instead of 3.76 in example 1.

The resulting formulation was surfactant free and chemically stable. This confirmed the formulation of example 3 was viable. However, it exhibited a flow time of 30 seconds.

Example 6

- 15 It was decided to use the formulation in example 2 as a base but to use 0.5% carboxymethyl cellulose sodium. The formulation volume was increased to 1000ml. The amount of each component was increased accordingly.

The formula in this example uses silicon dioxide (brand name Aerosil R972) alone and 0.5% carboxymethyl cellulose sodium to improve the flow time.

- 20 The formulation components and methods are as follows:

1. 5g Carboxymethyl cellulose sodium is dissolved in 300ml of water.
2. 1.072mg Ivermectin is dissolved in 50ml of medium chain mono-/di-glycerides (Capmul MCM.)

3. 1.8mg Sodium methyl paraben and 200mg sodium propyl paraben are dissolved in 500ml water, wherein 958mg sodium selenate and 12.568g cobalt EDTA are added under stirring.
4. 40g Levamisole HCl is added to the formulation from step 3 and 1g defoamer added under stirring.
5. 22.7g Oxfendazole is dispersed into the formulation resulting from step 4 under stirring.
6. Medium chain mono-/di-glycerides containing ivermectin (the formulation from step 2) is sorbed on 30g silicon dioxide (brand name Aerosil R972) using mortar and pestle.
7. The ivermectin-loaded silicon dioxide (brand name Aerosil R972) is dispersed into the formulation of step 5 under stirring.
10. 8. The formulation of Step 1 is added to that from step 7 under stirring.
9. 20ml of purified water is used to rinse the beaker; this is then added to the formulation from step 8.
10. The pH is adjusted to below 4, preferably 3.84 using 20%w/v citric acid solution.
15. 11. Volume is made up to 1L using purified water.

Testing of this formulation revealed a flow rate of 16 seconds through a Ford No. 4 cup suggesting the defoamer had no effect on the flow rate.

Example 7

- 20 In a further trial silicon dioxide (brand name Aerosil R972) was used and 0.5% carboxymethyl cellulose sodium was added for changing stability.

The formulation components and methods are as example 6 except:

- At step 10 the pH is set at 3.79 instead of 3.84 and 30%w/v citric acid solution is used instead of 20%w/v in example 6.
- At step 11 the volume is made up to 1000ml using purified water.

Testing of this formulation revealed a flow rate of 16 seconds confirming the defoamer had no effect on the flow rate.

Example 8

The following trial included ivermectin and xanthan gum.

5 The formulation components and methods comprised:

1. 6g Xanthan dissolved in 600ml water.
2. 3.216g Ivermectin dissolved separately in 150ml medium chain mono-/di-glycerides.
3. 5.4g Sodium methyl paraben and 600mg sodium propyl paraben sodium dissolved in 1800ml of water, to this 2.941g sodium selenate and 37.704g cobalt EDTA (14%) were
10 added under stirring.
4. 120g Levamisole HCL was added to the formulation of step 3 under stirring, to this 60g defoamer was added.
5. 68.1g Oxfendazole was dispersed into the formulation of step 4 under stirring.
6. The medium chain mono-/di-glycerides containing ivermectin was sorbed onto 90g
15 silicon dioxide (brand name Aerosil R972) using mortar and pestle.
7. Ivermectin loaded silicon dioxide (brand name Aerosil R972) was dispersed into the formulation from step 5 under stirring.
8. The formulation from Step 1 was added to that from step 7 under stirring.
9. 50ml of purified water was used to rinse the beaker. This was then added to the
20 formulation of step 8.
- 10 The pH was adjusted to below 4 preferably 3.71 using 30%w/v citric acid solution.
11. The volume was made up to 3000ml using purified water.

The resulting formulation had a reduced flow time of around 12 seconds.

Example 9

In a further trial abamectin and 0.2% xanthan gum was used.

The formulation components and methods are as example 9 except:

- 5 • At step 2, 3g abamectin is dissolved in 150ml medium chain mono-/di-glycerides (instead of ivermectin in example 9.)
- At step 7 the abamectin loaded silicon dioxide (brand name Aerosil R972) is dispersed into the formulation of step 5.
- At step 10 the pH is set at 3.81 instead of 3.71 in example 9.

10 Testing of this formulation revealed an easily dispersed composition with a reduced flow time of 12 seconds.

Example 10

In a further trial, a decreased amount of medium chain mono-/di-glycerides and silicon dioxide (brand name Aerosil R972) was used in combination with sodium benzoate and xanthum gum.

The formulation components and methods are as example 9 except:

- 15 • At step 1 xanthan gum was dissolved in 150ml of water instead of 600ml in example 9.
- At step 2 ivermectin was dissolved in 15ml of medium chain mono-/di-glycerides instead of 150ml in example 9.
- At step 3 sodium benzoate was added with sodium methyl paraben and sodium propyl paraben and dissolved in 250ml of water instead of 1800ml in example 9.
- 20 • At step 9 10ml of purified water was used to rinse the beaker instead of 50ml in example 9.
- At step 11 the volume was made up to 500ml as opposed to 3000ml in example 9.

Testing of this formulation revealed an incompatibility between the sodium benzoate and one of the ingredients in the formula.

Example 11

In this trial the formulation of example 10 was used to give a reduced quantity of medium chain
5 mono-/di-glycerides, silicon dioxide (brand name Aerosil R972) and xanthan gum. The sodium benzoate was omitted.

The formulation components and method are as example 10 except:

- At step 3 sodium benzoate is omitted.
 - At step 10 the pH is adjusted to 3.65 instead of 3.71 in example 10.
- 10 Testing this formulation revealed small oil droplets stuck to the inside of the walls of the container indicating not enough silicon dioxide (brand name Aerosil R972) was added to sorb the oil.

Example 12

In this trial the formulation is the same as example 11 except:

- 15
- At step 7 9g of silicon dioxide (Aerosil R972) was added.
 - At step 10 the pH is adjusted to 3.71 instead of 3.65 as in example 11.

Testing of this formulation revealed an easily dispersed formulation with a flow time of 14 seconds.

Example 13

20 In this trial the formulation is the same as example 12 except:

- At step 2 ivermectin is dissolved in 10ml medium chain mono-/di-glycerides instead of 15ml as in example 14.
- At step 7 6g of silicon dioxide (Aerosil R972) was added

Testing of this formulation revealed an easily dispersed formulation with a flow time of 14 seconds.

RESULTS

- The result of the trials determined example 12 was the best formulation on the basis it stably integrated two pharmaceutical actives in the formulation. The suspension was surfactant free and had a low sedimentation rate resulting in a formulation that can be stored without significant physical change. The formulation also had a reduced flow rate of around 15 seconds through a Ford No. 4 cup to allow for easy and effective administration of the formulation to animals.
- 10 In the examples a lipophilic active, ivermectin is firstly solubilised and then sorbed on a hydrophobic grade of silica. The surrounding aqueous solution contains levamisole, an active more stable at low pH. Levamisole salts (Levamisole HCl) are easily soluble in water. This method provides a physical and chemical separation between the sorbed ivermectin/silica and the surrounding solution or suspension containing the second or more active ingredients. It is envisaged that other materials may also be used as the sorbing medium. It will be appreciated that other combinations of actives may be used

PREFERRED FORMULATIONS

- Based on the development work described above, the following preferred formulations were developed. These illustrate the use of the method to make formulations incorporating 2, 3 or 4 actives together with optional mineral additives. These preferred formulations are administered to the animals orally at a rate of 1 ml per 5 kg live animal weight.

Oral Drench Containing Two Actives and Minerals

Name: ABAMECTIN – PRAZIQUANTEL DRENCH

<i>Materials</i>	<i>Amount/batch (g)</i>
Abamectin	500mg
Praziquantel	9.40gms
Sodium Selenate	476mg
Cobalt EDTA	6.284gm

Capmul MCM	15ml
Aerosil R972	9gms
Xanthan gum	1.250gms
Nipagin Sod.	900mg
Nipasol Sod.	100mg
Defoamer	10gms
Citric acid anhydrous	500mg
P. Water Q.S.	500ml

Procedure:

- 1 Dissolve Xanthan gum in 150 ml of water.
- 2 Dissolve Abamectin in Capmul MCM.
- 3 Dissolve Nipagin sodium and Nipasol sodium in water under heating separately. To this add sodium selenate, Cobalt EDTA and defoamer under stirring.
- 4 Disperse Praziquantel in step 3 under stirring.
- 5 Adsorb Capmul MCM containing Abamectin solution on Aerosil R972 using mortar and pestle.
- 6 Disperse Abamectin loaded Aerosil in step 4 under stirring.
- 7 Add Citric acid to step 6 under stirring.
- 8 Make the volume with water.
- 9 Check the pH.

Oral Drench Containing Two Actives without Minerals**Name: ABAMECTIN – PRAZIQUANTEL DRENCH**

<i>Materials</i>	<i>Amount/batch (g)</i>
Abamectin	500mg
Praziquantel	9.40gms
Capmul MCM	15.0ml
Aerosil R972	9.0gms
Xanthan gum	1.250gms
Nipagin Sod.	900mg
Nipasol Sod.	100mg

Defoamer	10gms
Citric acid anhydrous	500mg
P. Water Q.S.	500ml

Procedures

- 1 Dissolve Xanthan gum in 150 ml of water.
- 2 Dissolve Abamectin in Capmul MCM
- 3 Dissolve Nipagin sodium and Nipasol sodium in 250 ml of water under heating separately. To this add defoamer under stirring.
- 4 Disperse Praziquantel in step 3 under stirring
- 5 Adsorb Capmul MCM containing Abamectin solution on Aerosil R972 using mortar and pestle.
- 6 Disperse Adsorbed abamectin in step 4 under stirring.
- 7 Add Citric acid to step 6 under stirring.
- 8 Make the volume with water.
- 9 Check the pH

Oral Drench Containing Three Actives and Minerals

Name: 3 COMPONENT DRENCH

<i>Materials</i>	Amount/batch (g)
Levamisole HCl	20gms
Oxfendazole	11.35gms
Abamectin	500mg
Sodium Selenate eq. to selenium	0.2gms
Cobalt EDTA eq. to cobalt	0.88gms
Capmul MCM	15ml
Aerosil R972	9gms
Xanthan Gum	1.5gms
Nipagin Sod.	900mg
Nipasol Sod.	100mg
Defoamer	10gm

Citric acid anhydrous	1.4gm
P. Water Q.S.	to 500ml

PROCEDURES

- 1 Dissolve Xanthan Gum in 150ml of water
- 2 Dissolve Abamectin in Capmul MCM separately
- 3 Dissolve Nipagin sodium and Nipasol sodium in 250ml of water under heat. To this add Sodium Selenate and cobalt EDTA under stirring.
- 4 Add Levamisole HCl to step 3 under stirring. To this add Defoamer under stirring.
- 5 Disperse Oxfendazole in step 4 under stirring.
- 6 Adsorb Capmul MCM containing Abamectin on Aerosil R972 using mortar and pestle.
- 7 Disperse Abamectin loaded Aerosil in step 5 under stirring.
- 8 Add step 1 to step 7 under stirring.
- 9 Add Citric acid anhydrous to step 8 under stirring and check the pH.
- 10 Make the volume up to 500ml using purified water and stir further 30 minutes.

Oral Drench Containing Four Actives and Minerals**Name: 4 COMPONENT DRENCH**

<i>Materials</i>	<i>Amount/batch (g)</i>
Levamisole HCl	40gms
Oxfendazole	22.70gms
Abamectin	1.000gm
Praziquantel	18.80gms
Sodium Selenate eq. to selenium	0.4gms
Cobalt EDTA eq. to cobalt	1.76gms
Capmul MCM	30.00ml
Aerosil R972	18.00gms
Xanthan Gum	2.500gms
Defoamer	20gms
Nipagin Sod.	1.8gm
Nipasol Sod.	200mg

Citric acid anhydrous	2.8gms
P. Water Q.S.	1000ml

Procedures

- 1 Dissolve Xanthan Gum in 300ml of water
- 2 Dissolve Abamectin in Capmul MCM separately
- 3 Dissolve Nipagin sodium and Nipasol sodium in 500ml of water under heat. To this add Sodium selenate and cobalt EDTA under stirring.
- 4 Add Levamisole HCl to step3 under stirring. To this add Defoamer under stirring.
- 5 Disperse Oxfendazole in step 4 under stirring. To this add Praziquantel under stirring.
- 6 Adsorb Capmul MCM containing Abamectin solution on Aerosil R972 using mortar and pestle.
- 7 Disperse Abamectin loaded Aerosil in step 5 under stirring.
- 8 Add step 1 to step 7 under stirring.
- 9 Add citric acid anhydrous to step 8 and check the pH.
Make volume up to 1000ml using purified water and stir further 30 minutes.

The flow time of the 3 and 4 way drench disclosed above and the Triton™ 3-way drench marketed by Nufarm was compared. Flow time was determined using Sheen 406/4; ASTM

5 D1200 cup.

<i>S. No.</i>	<i>Sample</i>	<i>Flow Time (Seconds)</i>
1	Triton	33-36
2	3-way drench	14-17
3	4-way drench	16-18

3-way and 4-way drench formulations are suspension type of dosage forms. Some sediment formed upon standing at room temperature. The sedimented portion was easily redispersed upon shaking. There was no sign of cake formation.

10 FIELD TRIALS

The preferred formulations have also been shown to be highly efficacious in field use. The formulations were administered to animals as a drench at a rate of 1 ml per 5 kg animal weight.

Tables 1 and 2 below show the arithmetic and geometric mean total worm counts respectively for groups of sheep treated with the 3 and 4 active drenches. Tables 3 and 4 show the efficacies of each of the treatments relative to the controls using arithmetic and geometric means respectively.

- 5 Species identification indicated that the following species were present in the untreated control group: *Cooperia* species: 94% *C. curticei*, 4% *C. oncophora*, 2% *C. punctata*, *Trichostrongylus* species: 100% *T. colubriformis*.

Results demonstrate that both the 3 and 4 active drenches were highly effective against all species present in the trial. Efficacies of >99.9% were achieved against all parasites that were

- 10 present. Worm numbers in the control animals were high for all species that were present demonstrating that the animals were exposed to a very high parasite challenge.

Table 1: Arithmetic mean total worm counts for control and treated groups

Treatment	Control	4 active	3 active
<i>Ostertagia</i> (mature)	8275	0	0
<i>Ostertagia</i> (immature)	692	0	0
<i>T. axei</i> (mature)	1350	0	0
<i>T. axei</i> (immature)	67	0	0
<i>H. contortus</i> (mature)	5292	0	0
<i>H. contortus</i> (immature)	2150	0	0
<i>Trichostrongylus</i> spp (mature)	26983	0	0
<i>Trichostrongylus</i> spp (immature)	75	0	0
<i>Cooperia</i> (mature)	2258	0	0
<i>Cooperia</i> (immature)	58.4	0	0
<i>Strongyloides</i> (mature)	66.7	0	0
<i>Nematodirus</i> (mature)	267	0	0
<i>Nematodirus</i> (immature)	133.4	0	0
<i>Oesophagostomum</i>	38	0	0
<i>Chabertia</i>	12	0	0

<i>Trichuris</i>	17	0	0
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Table 2: Geometric mean total worm counts for control and treated groups

Treatment	Control	4 active	3 active
<i>Ostertagia</i> (mature)	7660 ^a	0 ^b	0 ^b
<i>Ostertagia</i> (immature)	140 ^a	0 ^b	0 ^b
<i>T. axei</i> (mature)	858 ^a	0 ^b	0 ^b
<i>T. axei</i> (immature)	21 ^a	0 ^b	0 ^b
<i>H. contortus</i> (mature)	3343 ^a	0 ^b	0 ^b
<i>H. contortus</i> (immature)	1009 ^a	0 ^b	0 ^b
<i>Trichostrongylus</i> spp (mature)	20254 ^a	0 ^b	0 ^b
<i>Trichostrongylus</i> spp (immature)	19.7 ^a	0 ^b	0 ^b
<i>Cooperia</i> (mature)	1281 ^a	0 ^b	0 ^b
<i>Cooperia</i> (immature)	11 ^a	0 ^a	0 ^a
<i>Strongyloides</i> (mature)	18.7 ^a	0 ^b	0 ^b
<i>Nematodirus</i> (mature)	20.6 ^a	0 ^b	0 ^b
<i>Nematodirus</i> (immature)	53.8 ^a	0 ^b	0 ^b
<i>Oesophagostomum</i>	33 ^a	0 ^b	0 ^b
<i>Chabertia</i>	6 ^a	0 ^b	0 ^b
<i>Trichuris</i>	15 ^a	0 ^b	0 ^b

^{ab} = means with different superscripts within the same row are statistically different from each other.

5 Table 3: Treatment efficacies based on group arithmetic mean total worm counts.

Treatment	4 active	3 active
<i>Ostertagia</i> (mature)	>99.9%	>99.9%
<i>Ostertagia</i> (immature)	>99.9%	>99.9%
<i>T. axei</i> (mature)	>99.9%	>99.9%
<i>T. axei</i> (immature)	>99.9%	>99.9%
<i>H. contortus</i> (mature)	>99.9%	>99.9%
<i>H. contortus</i> (immature)	>99.9%	>99.9%

<i>Trichostrongylus</i> spp (mature)	>99.9%	>99.9%
<i>Trichostrongylus</i> spp (immature)	>99.9%	>99.9%
<i>Cooperia</i> (mature)	>99.9%	>99.9%
<i>Cooperia</i> (immature)	>99.9%	>99.9%
<i>Strongyloides</i> (mature)	>99.9%	>99.9%
<i>Nematodirus</i> (mature)	>99.9%	>99.9%
<i>Nematodirus</i> (immature)	>99.9%	>99.9%
<i>Oesophagostomum</i>	>99.9%	>99.9%
<i>Chabertia</i>	>99.9%	>99.9%
<i>Trichuris</i>	>99.9%	>99.9%

Table 4: Treatment efficacies based on group geometric mean total worm counts.

Treatment	4 active	3 active
<i>Ostertagia</i> (mature)	>99.9%	>99.9%
<i>Ostertagia</i> (immature)	>99.9%	>99.9%
<i>T. axei</i> (mature)	>99.9%	>99.9%
<i>T. axei</i> (immature)	>99.9%	>99.9%
<i>H. contortus</i> (mature)	>99.9%	>99.9%
<i>H. contortus</i> (immature)	>99.9%	>99.9%
<i>Trichostrongylus</i> spp (mature)	>99.9%	>99.9%
<i>Trichostrongylus</i> spp (immature)	>99.9%	>99.9%
<i>Cooperia</i> (mature)	>99.9%	>99.9%
<i>Cooperia</i> (immature)	>99.9%	>99.9%
<i>Strongyloides</i> (mature)	>99.9%	>99.9%
<i>Nematodirus</i> (mature)	>99.9%	>99.9%
<i>Nematodirus</i> (immature)	>99.9%	>99.9%
<i>Oesophagostomum</i>	>99.9%	>99.9%
<i>Chabertia</i>	>99.9%	>99.9%
<i>Trichuris</i>	>99.9%	>99.9%

STABILITY TRIALS

It has also been demonstrated that the formulations made according to this method are stable using accelerated testing in elevated temperature conditions. Batch samples were tested for 2, 3, and 4 active drenches.

5 Stability results summary of trials

Stress conditions: 55°C for 2, 4 weeks

<i>Batch No.</i>	<i>Condition</i>	<i>Ivermectin</i>	<i>% Recovery</i>	<i>Oxfendazole</i>	<i>% Recovery</i>	<i>Levamisole HCl</i>	<i>% Recovery</i>
Example 1	55°C, 4week	0.083	93%	2.08	109%	3.78	97%
	55°C, 2week	0.088	99%	2.07	108%	3.90	101%
	4°C	0.089	100%	1.91	100%	3.88	100%
Example 2	55°C, 4week	0.087	95%	2.06	99%	3.88	99%
	55°C, 2week	0.090	98%	2.06	100%	3.99	102%
	4°C	0.092	100%	1.73	100%	3.91	100%
Example 3	55°C, 4week	0.095	97%	2.33	110%	4.15	100%
	55°C, 2week	0.096	98%	2.24	106%	4.18	101%
	4°C	0.098	100%	2.12	100%	4.13	100%
Example 4	55°C, 4week	0.079	93%	1.85	97%	3.91	102%
	55°C, 2week	0.079	96%	1.75	98%	3.97	104%
	4°C	0.088	100%	1.91	100%	3.82	100%
Example 5	55°C, 4week	0.087	99%	2.12	104%	3.80	98%
	55°C, 2week	0.090	102%	2.13	104%	4.05	104%
	4°C	0.088	100%	2.04	100%	3.89	100%
Example 6	55°C,	0.087	84%	2.46	102%	3.84	96%

	4week						
	55°C, 2week	0.090	87%	2.42	100%	3.76	94%
	4°C	0.103	100%	2.41	100%	4.00	100%
Example 7	55°C, 4week	0.096	93%	2.39	102%	3.63	95%
	55°C, 2week	0.099	96%	2.36	101%	3.79	99%
	4°C	0.103	100%	2.34	100%	3.83	100%
Example 8	4°C	0.107	100%	2.36	100%	4.02	100%
	55°C, 2week	0.103	96%	2.37	100%	3.97	99%
	55°C, 4week	0.099	93%	2.38	101%	3.95	98%
Example 12	4°C	0.109	100%	2.51	100%	4.23	100%
	55°C, 2week	0.105	96%	2.50	100%	4.17	99%
	55°C, 4week	0.101	93%	2.58	103%	4.25	100%
Example 13	4°C	0.100	100%	2.39	100%	4.22	100%
	55°C, 2week	0.099	99%	2.43	102%	4.12	98%
	55°C, 4week	0.098	98%	2.43	102%	4.05	96%
Example 9	4°C	0.103	100%	2.43	100%	4.17	100%
	55°C, 2week	0.101	98%	2.40	99%	4.08	98%
	55°C, 4week	0.096	93%	2.45	101%	3.99	96%

PREFERRED FORMULATIONS STABILITY RESULTS

Stability results of 2 actives drench

Stress conditions: 55°C for 2-4 weeks

Batch No.	Condition	Abamectin	% Recovery	Praziquantel	% Recovery
011202	4°C	0.089	100%	1.97	100%

(Without Minerals)	55°C, 2week	0.089	100%	1.97	100%
	55°C, 4week	0.089	100%	1.94	99%
011202	4°C	0.079	100%	1.83	100%
(With Minerals)	55°C, 2week	0.079	100%	1.77	97%
	55°C, 4week	0.079	100%	1.79	98%

Stability results of 3 actives drench

Stress conditions: 55°C for 2-4 weeks

5

Batch No.	Condition	Abamectin	% Recovery	Oxfendazole	% Recovery	Levamisole HCl	% Recovery
DRE001 / 04	4°C	0.108	100%	2.55	100%	4.71	100%
	55°C, 2week	0.102	94%	2.55	100%	4.67	100%
	55°C, 4week	0.099	92%	2.60	102%	3.71	100%

Stability results of 4 actives drench

10 Stress conditions: 55°C for 2-4 weeks

Batch No.	Condition	Ivermectin	% Recovery	Oxfendazole	% Recovery	Levamisole HCl	% Recovery	Praziquantel	% Recovery
050802	4C	0.124	100%	2.60	100%	4.47	100%	1.99	100%
	55C, 2week	0.133	105%	2.52	97%	4.42	99%	1.96	98%
	55C, 4week	0.139	107%	2.62	101%	4.42	99%	1.96	98%
060802	4C	0.111	100%	2.33	100%	4.10	100%	1.87	100%
	55C, 2week	0.100	90%	2.33	100%	4.05	99%	1.86	99%
	55C, 4week	0.100	90%	2.37	102%	4.01	98%	1.88	101%
070802	4C	0.114	100%	2.13	100%	4.68	100%	2.09	100%
	55C, 2week	0.116	102%	2.15	101%	4.65	99%	2.10	100%
	55C,	0.113	99%	2.14	100%	4.63	99%	2.09	100%

	4week								
080802	4C	0.099	100%	2.08	100%	3.95	100%	1.84	100%
	55C, 2week	0.098	99%	2.07	100%	3.98	101%	1.63	95%
	55C, 4week	0.098	99%	2.06	99%	4.01	102%	1.59	93%
090802	4C	0.104	100%	2.46	100%	3.21	100%	2.05	100%
	55C, 2week	0.104	100%	2.42	98%	3.19	99%	2.06	100%
	55C, 4week	0.099	95%	2.34	95%	3.20	100%	2.00	98%
100802	4C	0.082	100%	3.85	100%	4.07	100%	1.85	100%
	55C, 2week	0.081	99%	3.85	100%	4.04	99%	1.80	97%
	55C, 4week	0.083	101%	3.95	103%	4.04	99%	1.85	100%
110802	4C	0.086	100%	2.52	100%	4.39	100%	2.01	100%
	55C, 2week	0.086	100%	2.53	100%	4.32	98%	2.01	100%
	55C, 4week	0.088	102%	2.59	103%	4.30	98%	2.05	102%

As can be seen from the above trials the methods of the present invention and the formulations made from those methods, allow the stable integration of multiple actives within a single formulation. The solubilisation of the active in a solvent and the subsequent adsorption onto a sorbing medium provide effective protection for the active from any adverse conditions within the liquid in which the active-loaded sorbing medium is dispersed. As a result the liquid can be formulated to suit the requirements of the actives that may include therein. As a result the actives may be stably integrated within the formulation. This allows the co-administration of the actives and the resultant benefits in terms of cost savings and convenience to be enjoyed.

We Claim:

- 1) A method of manufacturing a pharmaceutical formulation comprising the steps:
 - a) Dissolving an active in a solvent;
 - b) Sorbing the solvent containing active composition on to a sorbing medium; and then
- 5 c) Dispersing the sorbing medium loaded with the solvent composition in a liquid.
- 2) A method as claimed in claim 1, wherein the active is a lipophilic active.
- 3) A method as claimed in claim 2, wherein the lipophilic active is selected from the group including the avermectins and the milbemycins.
- 4) A method as claimed in any previous claim, wherein the liquid is an aqueous vehicle.
- 10 5) A method as claimed in claim 1, wherein the solvent is selected from oils and organic solvents.
- 6) A method as claimed in claim 5, wherein the solvent is selected from medium chain mono-/di-glycerides (Capmul MCM) in the range of 0.1-10% preferably between 2-4%.
- 7) A method as claimed in any previous claim, wherein the liquid optionally includes one or
- 15 more medicaments selected from the group including vitamins, minerals, anthelmintics or antigens.
- 8) A method as claimed in claim 7, wherein the minerals are selected from selenium salts, cobalt salts, copper salts, zinc salts, iodine salts and their chelates.
- 9) A method as claimed in claim 8 wherein the minerals are selected from sodium selenate and
- 20 cobalt EDTA.
- 10) A method as claimed in claim 7 wherein the anthelmintics are selected from the group including thiazole derivatives such as a levamisole salt and benzimidazole derivatives such as albendazole, oxfendazole, fenbendazole, mebendazole and acylated quinoline such as praziquantel, and benzenesulphonamide such as a clorsulon and closantel.

- 11) A method as claimed in any previous claim wherein the sorbing medium is selected from magnesium aluminometasilicate, cellulose, microcrystalline cellulose, diatomaceous earth, montmorillonite, bentonite, titanium dioxide, amorphous silicon dioxide, colloidal silicon dioxide (Aerosil), calcium carbonate, talc ($\text{SiO}_2 + \text{MgO}$), attapulgite (silicon, aluminium and iron oxides clay), kaolin (aluminium silicate) preferably Aerosil more preferably Aerosil R972.
- 12) A method as claimed in any previous claim, wherein the liquid optionally comprises further excipients including but not limited to preservatives, suspending agents, buffering agents, antifoaming agents and the like.
- 10 13) A pharmaceutical formulation capable of dilution and capable (with or without dilution) of being administered to an animal, said formulation comprising:
- a) an active dissolved in a suitable solvent to form a solution and sorbed on to a sorbing medium; and
 - b) optionally including a liquid diluent.
- 15 14) A formulation as claimed in claim 13, wherein the active is a lipophilic active.
- 15) A formulation as claimed in claim 14, wherein the active is selected from the group including the avermectins and the milbemycins.
- 16) A formulation as claimed in claim 15, wherein the solvent is selected from oils and organic solvents.
- 20 17) A formulation as claimed in claim 16, wherein the solvent is medium chain mono-/di-glycerides (Capmul MCM).
- 18) A formulation as claimed in claim 13, wherein the liquid diluent comprises an aqueous vehicle.
- 19) A formulation as claimed in claim 13, wherein the aqueous vehicle optionally includes one or more additional medicaments selected from the group including vitamins, minerals, anthelmintics or antigens.
- 25

- 20) A formulation as claimed in claim 19, wherein the medicament is either soluble and/or dispersible in the liquid.
- 21) A formulation as claimed in claim 19 wherein the minerals are selected from wherein the minerals are selected from selenium salts, cobalt salts, copper salts, zinc salts, iodine salts and their chelates.
- 22) A formulation as claimed in claim 19 wherein the minerals are selected from sodium selenate and cobalt EDTA.
- 23) A formulation as claimed in claim 19 wherein the anthelmintics are selected from the group including thiazole derivatives such as a levamisole salt and benzimidazole derivatives such as albendazole, oxfendazole, fenbendazole, mebendazole and acylated quinoline such as praziquantel, and benzenesulphonamide such as a clorsulon and closantel.
- 24) A formulation as claimed in any of claims 13 to 23, which additionally includes preservatives, suspending agents, buffering agents, antifoaming agents and the like.
- 25) A method of medical treatment comprising administering a formulation as described in the preceding claims to an animal.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/NZ2003/000272

A. CLASSIFICATION OF SUBJECT MATTERInt. Cl. ⁷: A61K 47/02, 47/04, 47/38, 35/70, 31/365; A61P 33/14, 33/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
 DWPI, CAS : Keywords - Avermectin, milbemycin, abamectin, sorb, absorb, absorption, magnesium aluminometasilicate, cellulose, diatomaceous earth, betonite, titanium dioxide, silicon dioxide, kaolin, calcium carbonate, talc, attapulgite and related terms

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4678774 A (PUTTER et al.) 7 July 1987 See col. 2 lines 23-40, col. 3 lines 9-34 and lines 55-63	1-25
X	WO 2001/060409 A (MERIAL LTD) 23 August 2001 See page 6 line 1 - page 8 line 3; claims 2, 4, 8 and 22	1-25
X	Patent Abstract of Japan, JP 05-085902 A (NIPPON KAYAKU CO. LTD) 6 April 1993 Abstract	1-25



Further documents are listed in the continuation of Box C



See patent family annex

<p>* Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>		<p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p>
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/NZ2003/000272

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report			Patent Family Member			
US	4678774	NONE				
WO	2001/060409	AU 33738/01	BR 0108449	CA 2400317		
		CZ 20022772	EP 1263467	US 2003007958		
JP	5085902	NONE				
						END OF ANNEX